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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/627,787	UHLMANN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 October 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,4-6 and 8-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *27 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered on 8/14/03.

Claims 1-26 are pending.

Claims 3, 6, and 7 were withdrawn from consideration in Paper No. 15 as being drawn to nonelected species. Applicant timely traversed in Paper No. 14.

Finality of the previous Office Action is withdrawn in view of the new grounds of rejection set forth below. It is noted that the Lucas reference anticipates claim 6 inasmuch as it teaches an aryl conjugate comprising two esterified fatty acids of less than 500 D. As such claim 6 is rejoined

Claims 1, 2, 4-6, and 8-26, and the species of the invention wherein the molecule to be transported is an oligonucleotide or a compound of less than 500 D are under consideration in this Office Action.

Information Disclosure Statements

Properly initialed copies of the information disclosure statements filed 12/22/00, 8/22/01, and 10/25/01 are included in this Action.

Rejections Withdrawn

The rejection of claims 22-24 under 35 USC 112, first paragraph is withdrawn.

The rejection of claims 1, 2, 4, 5, 10, and 22-25 as anticipated by Iyer is withdrawn in view of Applicant's amendments.

The rejections of claims 11, 12, and 15 as anticipated by Cook ,and claims 11, 13, and 14 as obvious over Cook, are withdrawn in view of Applicant's amendments and arguments.

The rejection of claims 1, 2, 8, 24, and 25 as anticipated by Cuthbertson, and claim 26 as obvious over Cuthbertson, are withdrawn in view of Applicant's submission of a translation of the foreign priority document (DE 199 35 302.6).

The rejections of claims 16-20 over Peyman in combination with other references are overcome by Applicant's statement of common ownership demonstrating that the patent of Peyman et al is commonly assigned with the instant application.

Claim Objections

Claim 11 and dependents are objected to because they recite the phrase reactive function group for the reasons applied to claims 1 and 12 in the previous Action. The claims would be clearer if the word "function" was deleted, as in claim 12.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite to the extent that it depends from claim 1, because none of the structures listed in claim 9 meets the claim 1 limitation wherein R1 must be a C5-C23 alkyl radical.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-6, and 10-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4-6, and 10-26 are drawn to the genus of conjugates comprising an aryl radical of formula I as set forth in claim 1. The "aryl" portion of the radical may be any group containing at least on ring having aromatic character. The remaining constituents of the radical ("X", "Y", and "R1") are given limiting definitions in the claims. So the breadth of the claimed genus is equal to the breadth of the group containing at least one ring having aromatic character.

The specification at page 4, line 25 to page 5, line 34 indicates that the essence of the invention is that "aryl ester conjugates of a certain structure" have "advantageous properties" such as improved duration and efficiency of cellular uptake, and improved intracellular distribution. At page 6, lines 1-14 the specification discloses that arylester-oligonucleotide conjugates according to formula I were known in the prior art (Iyer et al (Bioorg. Med. Chem. 7(7):

871/876, 1997)), but "in contrast to the conjugates according to the instant invention, no accelerated uptake of the oligonucleotides into the cells and likewise no changed intracellular distribution of the oligonucleotides have been found for these prodrugs."

Given the teachings of the specification, it is clear that Applicant considers the invention to be the discovery of an aryl radical conjugate that affords improved cellular uptake and intracellular distribution characteristics. However, while the specification teaches that "all aryl conjugates of a certain structure" will provide the advantages of the invention, the specification fails to adequately describe that "certain structure". For example, the specification fails to teach why the structures of Iyer (1997), while falling within the genus set forth in claim 1, fail to have the improved functional characteristics that Applicant associates with the invention.

The specification reduces to practice 11 species of the invention in Figs. 2a and 2b. These structures differ from the structure of Iyer in that the molecule to be delivered is linked to the aryl group via a carbonyl or a thioamide group. This is the only structural element that these compounds have in common that is absent from the compounds of Iyer, i.e. what structural component is required for the improved cellular uptake and intracellular distribution characteristics that are the essence of the invention.

Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The 11 species reduced to practice in the specification correspond to the subgenus recited in claim 8 and dependents, i.e. those conjugates in which the molecule to be transported is attached to the aryl group via a carbonyl or thioamide linkage. These species are deemed to provide an adequate written description of that subgenus. However, the only disclosed examples of the genus of conjugates that lack the carbonyl or thioamide (i.e. the conjugates of Iyer), do not appear to have the functional characteristics that Applicant associates with the invention. The specification fails to reduce any of these structures to practice and fails to teach what "certain structure" of these aryl conjugates is required for the functional characteristics that Applicant perceives as the contribution over the prior art. In the absence of any reduction to practice or teaching of a correlation between any required structural characteristic of these aryl radicals and the functional characteristics of the conjugates, this portion of the genus is not adequately described, and one of skill in the art could not conclude that Applicant was in possession of the claimed

genus of aryl radicals invention at the time of filing. This rejection can be overcome by requiring the carbonyl or thioamide linkage as set forth in claim 8.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 11, 12, 16-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Lucas et al (5,698,411, issued 12/16/1997).

Lucas teaches compositions for assaying enzyme activity in intact cells. The compositions comprise a conjugate between an aryl moiety and one or more leaving groups. See abstract. The leaving groups may be e.g. lipids or fatty acids of less than 500 Daltons. See abstract; column 9, line 16 to column 10, line 2; and column 23, lines 43-65. See also attached search result showing an aryl group with two amide groups attached which anticipates claims 1 and 6 when X=N. Note also that the analogous compound comprising fatty acid esters would anticipate claim 1 when, X=O. In this rejection, one fatty acid or amide moiety accounts for R1 and the other is considered to be the molecule to be delivered. The compositions are transported into both human and tumor cells. See paragraphs 113 and 107. The compositions may be admixed to provide proper osmolality and may contain additives such as enzyme inhibitors. See column 28, lines 15-41. Claims 24-26 are included in this rejection because the

compositions of Lucas meet the physical characteristics required by these claims.

Thus Lucas anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-6, 10, and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer et al (Bioorg. Med. Chem. 7(7): 871/876, 1997), in view of Iyer et al (Bioorg. Med. Chem. 4(20): 2471-2476, 1994), and Iyer et al (Bioorg. Med. Chem. 6(16): 1917-1922, 1996).

Iyer(1997) teaches phosphorothioate or phosphodiester oligonucleotides comprising acyloxyaryl conjugates at the internucleotide linkages. See Fig. 2, and Scheme 1 on page 872. The oligonucleotides are intended to be delivered to cells. See page 871, lines 1-6 of first paragraph.

Iyer does not teach a conjugate comprising a group corresponding to instantly claimed group R1 which is a C5-C22 alkyl radical. Instead Iyer teaches a t-butyl R1 group. See scheme 1 on page 872. Iyer (1997) is silent as to the pH at which reaction between the molecule to be transported and the aryl radical is carried out.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the composition of Iyer (1997) by substituting C5-C22 alkyl radicals for the isobutyl radical, because they differ from the group of Iyer only by the addition of -CH2- groups, and because the stated function of the groups of Iyer is to provide lipophilicity to the oligonucleotide for improved cellular uptake. See Iyer (1994) paragraph bridging pages 2471 and 2472, and Iyer (1996) page 1917, lines 9-12. One of ordinary skill in the art would expect the instant C5-C22 groups to provide this function, so substitution would preserve the stated function of the t-butyl group of Iyer. MPEP 2144.09 states that a prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). Further, compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

Pertinent to claims 22 and 23, the Iyer references teach admixing phosphorothioate and phosphodiester versions of the conjugates as well as

adding an aqueous buffer excipient. See (paragraph bridging pages 873 and 874.

Claims 24 and 25 are included in this rejection because the compositions of Iyer meet the physical characteristics required by these claims. For example, absent evidence to the contrary, the modified oligonucleotides could be considered to be diagnostic compositions as required by claim 25, because they would be useful in hybridization assays to detect their target nucleic acids.

Pertinent to claim 26, Iyer (1997) does not explicitly teach the organization of the compositions into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the compositions into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer (1997), Iyer (1996), and Iyer (1994) as applied to claims 1, 2, 4, 5, 10, 11, 13-15, and 22-26 above, and further in view of either one of Yamamoto et al (Genetics (1992) 131(4): 811-819), or White et al (Antimicrob. Agents and Chemother. (1997) 41(12): 2699-2704).

The Iyer references can be combined to render obvious oligonucleotides with acyloxyaryl modifications, intended for delivery to cells. The purposes of the modification include improving cellular uptake by increasing the hydrophobic character of the oligonucleotides, and increasing stability by inhibiting nucleolytic

degradation. See page 1917, lines 11-16 of Iyer (1996), page 2472, lines 3-8 of Iyer (1994).

These references do not explicitly disclose a method of delivering oligonucleotides across a cell membrane, particularly to bacterial or yeast cells.

Yamamoto teaches a method of delivering antisense oligonucleotides to yeast cells.

White teaches a method of delivering antisense oligonucleotides to E. coli cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the antisense oligonucleotides of Yamamoto or White as taught by Iyer (1997) in order to improve subsequent cellular oligonucleotide uptake and stability.

Thus the invention as a whole was prima facie obvious.

Claims 16-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer (1997), Iyer (1996), and Iyer (1994) as applied to claims 1, 2, 4, 5, 10, 11, 13-15, and 22-26 above, and further in view of Higgins et al (PNAS (1993) 90: 9901-9905).

The Iyer references can be combined to render obvious oligonucleotides with acyloxyaryl modifications, intended for delivery to cells. The purposes of the modification include improving cellular uptake by increasing the hydrophobic character of the oligonucleotides, and increasing stability by inhibiting nucleolytic degradation. See page 1917, lines 11-16 of Iyer (1997).

These references do not explicitly disclose delivery across a cell membrane, particularly to a human cell (claim 20) or a tumor cell (claim 21).

Higgins teaches a method of delivering antisense oligonucleotides to human tumor cells in vitro and to mouse tumor cell in vivo. The oligonucleotides administered in vivo were prepared in phosphate buffered saline and are considered to be a pharmaceutical composition. See abstract; "Tumorigenicity Assays" on pages 9901 and 9902; Table 1 on page 9902; and Fig. 2 on page 9903.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the oligonucleotides of Higgins as taught the Iyer references in order to improve delivery and stability of the oligonucleotides.

Thus the invention as a whole was prima facie obvious.

Claims 11, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lucas et al (5,698,411, issued 12/16/1997).

Lucas teaches compositions for assaying enzyme activity in intact cells. The compositions comprise a conjugate between an aryl moiety and one or more leaving groups. See abstract. The leaving groups may be e.g. lipids or fatty acids. See abstract; column 9, line 16 to column 10, line 2; and column 23, lines 18 to column 24, line 10. See also attached search result showing an aryl group with two amide groups attached which anticipates claim 1 when X=N. Note also that the analogous compound comprising fatty acid esters would anticipate claim 1 when, X=O. In this rejection, one fatty acid or amide moiety accounts for R1 and the other is considered to be the molecule to be delivered.

Lucas is silent as to the pH of the reaction conditions under which the aryl moiety and the leaving group are joined, however the pH of the reaction is

considered to be a result effective variable that is routinely optimized. Absent evidence to the contrary, it would have been obvious to perform the reaction at pH 7.0.

Claims 1, 2, 4, 5, 10, 11, 12, 15-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lucas et al (5,698,411, issued 12/16/1997) in view of Pitt et al (Journal of General Microbiology (1969), 56(3), 321-9).

Lucas teaches compositions for assaying enzyme activity in intact cells. The compositions comprise a conjugate between an aryl moiety and one or more leaving groups. See abstract. The leaving groups may be e.g. polysaccharides, oligopeptides, lipids, fatty acids, nucleotides, polynucleotides, and combinations thereof. See abstract; column 9, line 16 to column 10, line 2; and column 23, lines 18 to column 24, line 10. See also attached search result showing an aryl group with two amide groups attached which renders obvious claim 1 when X=N. Note also that the analogous compound comprising fatty acid esters would renders obvious claim 1 when, X=O. Instant claims requiring that the delivered molecule must be a polynucleotide, nucleotide, or a polysaccharide are obvious in view of compositions comprising a fatty acid or amide leaving group as well as a polynucleotide nucleotide, or polysaccharide leaving group as allowed for at column 9, line 16 to column 10, line 2. The fatty acid or amide moiety accounts for R1. See attached search result and column 23, lines 57-65. Nucleic acid attachment is exemplified at the nucleobase via an amine group, and at a 5' phosphate position, but other sites of attachment are considered to be obvious

variants to one of ordinary skill in the art. Similarly modification of the nucleic acid to provide other types of reactive groups as listed in instant claim 12 is considered to be obvious in view of the teachings of Lucas from column 24, line 566 to column 25, line 9, which discloses modification of the leaving group (i.e. nucleic acid) for attachment to an indicator group (e.g. rhodamine or fluorescein). The compositions are transported into both human and tumor cells. See paragraphs 113 and 107. The compositions may be admixed to provide proper osmolality and may contain additives such as enzyme inhibitors. See column 28, lines 15-41. Claims 24-26 are included in this rejection because the compositions of Lucas meet the physical characteristics required by these claims.

Lucas does not teach conjugates comprising oligonucleotides.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use oligonucleotides in the invention of Lucas. One would have been motivated to do so in order to assay a given cell for the activity of a nuclease and an esterase. For example, Pitt teaches that various hydrolytic enzymes such as RNases and esterases are released from cytoplasmic organelles as a result of viral infection, so it would have been obvious to use the invention of Lucas to assay simultaneously both these activities as an indicator of infection or of organelle integrity. It would have been obvious to substitute an oligonucleotide for a polynucleotide, as these compounds are art recognized equivalents, i.e. they are both degraded by nucleases. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be

substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Claims 8, 11-14, and 16-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lucas et al (5,698,411, issued 12/16/1997) in view of either Choi et al (US patent 5,820,873, issued 10/13/98) or Norden et al (US Patent 6,228,982, issued 5/8/01).

Lucas teaches compositions for assaying enzyme activity in intact cells. The compositions comprise a conjugate between an aryl moiety and one or more leaving groups. See abstract. The leaving groups may be e.g. polysaccharides, oligopeptides, lipids, fatty acids, nucleotides, polynucleotides, and combinations thereof. See abstract; column 9, line 16 to column 10, line 2; and column 23, lines 18 to column 24, line 10.

Lucas does not teach an aryl group of formula I separated from the molecule to be transported by a carbonyl or thioamide linker.

It is apparent from the teachings of Choi or Norden that it is routine in the art to join two moieties of interest through the use of an intervening linker. For example, Choi teaches that polyethylene glycol can be joined to a ceramide linkage via a linker, and further notes that the linker may be a carbonyl group. See e.g. paragraph bridging columns 5 and 6, especially column 6, lines 1-7 which indicates that the identity of the linker group is a matter of design choice.

Similarly, Norden teaches that ligands may be linked to peptide nucleic acids via any of a number of linkages including a thioamide linkage. See column 2, lines 18-22.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of any of the preceding rejections to include a carbonyl or thioamide linker between the aryl group and the molecule to be transported because the prior art teaches that the use of linkers is routine in the art, the use of both carbonyl and thioamide linkages was well known, and the selection of a particular linker is a matter of design choice.

Claims 8, 10, 11, 12, 15-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lucas et al (5,698,411, issued 12/16/1997) in view of Pitt et al (Journal of General Microbiology (1969), 56(3), 321-9) and either Choi et al (US patent 5,820,873, issued 10/13/98) or Norden et al (US Patent 6,228,982, issued 5/8/01).

The teachings of Lucas and Pitt are described above and can be combined to render obvious conjugates between an aryl moiety and one each of an oligonucleotide and a fatty acid ester.

Lucas does not teach linkage of the oligonucleotide to the aryl group through a carbonyl or thioamide linkage.

It is apparent from the teachings of Choi or Norden that it is routine in the art to join two moieties of interest through the use of an intervening linker. For example, Choi teaches that polyethylene glycol can be joined to a ceramide

linkage via a linker, and further notes that the linker may be a carbonyl group. See e.g. paragraph bridging columns 5 and 6, especially column 6, lines 1-7 which indicates that the identity of the linker group is a matter of design choice. Similarly, Norden teaches that ligands may be linked to peptide nucleic acids for transport via any of a number of linkages including a thioamide linkage. See column 2, lines 18-22.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of any of the preceding rejections to include a carbonyl or thioamide linker between the aryl group and the molecule to be transported because the prior art teaches that the use of linkers is routine in the art, the use of both carbonyl and thioamide linkages was well known, and the selection of a particular linker is a matter of design choice.

Conclusion

No claim is allowed. Claim 9 is free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at 703-306-3217. The official central fax number is 703-872-9306. Inquiries of a general nature or

relating to the status of the application should be directed to the Patent Analyst

Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

DAVET.NGUYEN
PRIMARY EXAMINER